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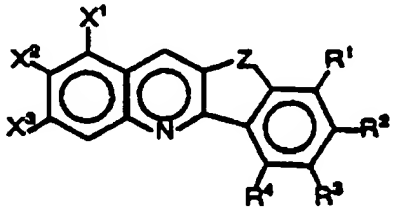

(I)

(57) Abstract

The present invention relates to certain substituted tetracyclic fused quinoline derivatives of formula (I), wherein R^1 is hydrogen, hydroxy, fluoro, chloro, bromo, iodo, methoxy or amino; R^2 is hydrogen, hydroxy, methoxy or amino; R^3 is hydrogen, hydroxy, methoxy, methoxymethoxy, amino, $-OCONH_2$, [2(5H)-3,4-dihydro-3-oxyfuranonel, 2-hydroxyethoxy, 2-aminoethoxy, 3-hydroxypropoxy or 3-aminopropoxy; or taken together with R^2 or R^4, methylenedioxy or ethylenedioxy; R^4 is hydrogen, hydroxy or amino; Z is $-CH_2-$, -O- or -NH-; and a) X^1 is hydrogen; X^2 is hydrogen, hydroxy, fluoro, chloro, bromo, iodo or methoxy; and X^3 is hydrogen or hydroxy; or b) X^2 taken together with X^3 is methylenedioxy or etylenedioxy, and X^1 is hydrogen or a pharmaceutically acceptable salt thereof provided that: i) at least one of R^1 through R^4 is other than hydrogen; ii) when R^1 is methoxy, R^2 is hydroxy or methoxy, R^3 is hydrogen or methoxy and R^4 is hydrogen; iii) when R^2 is hydroxy, methoxy or amino, R^3 is hydrogen, hydroxy or methoxy, and R^4 is hydrogen; iv) when R^4 is hydroxy or amino, R^1 and R^3 are hydrogen and R^2 is hydroxy or amino; and v) when R^1 is fluoro, chloro, iodo or amino, R^2 is hydrogen, hydroxy or methoxy, R^3 is hydrogen, hydroxy or methoxy and R^4 is hydrogen and the use of these compounds as topoisomerase inhibitors and antitumor agents.

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CYCLIC ANTITUMOR COMPOUNDS

The present invention relates to certain substituted tetracyclic fused quinoline derivatives which have topoisomerase inhibition and antitumor activity.

BACKGROUND OF THE INVENTION

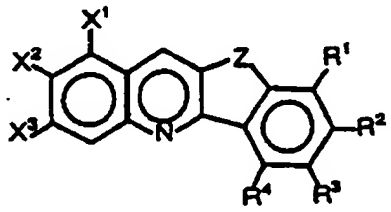
Before a living cell can reproduce, its DNA strands must unwind from their normal coiled configurations and assume a topology favorable for replication. To allow this unwinding the enzymes known as topoisomerases serve to introduce "swivels" in DNA strands. Without such a mechanism the DNA could not replicate, and hence the cell could not reproduce and proliferate. For detailed explanations of the topoisomerase function see A. Lehninger, *Principles of Biochemistry*, 813, Worth Publishers, New York (1982); L. F. Liu, "DNA Topoisomerases," *CRC Critical Review in Biochemistry*, 1-24, 15 (1983) and H Vosberg, "DNA Topoisomerases: Enzymes that Control DNA Conformation," *Current Topics in Microbiology and Immunology*, 19, Springer-Verlag, Berlin (1985). It has been recognized for some time that cell proliferation might be controlled by inhibition of topoisomerases and that such control might be particularly useful in halting the spread of tumors and related malignancies and ultimately destroying them. See E. Nelson, *et al.*, *Proc. Nat. Acad. Sci. U.S.A.*, 81, 1361 (1984).

On the basis of mechanism of action, topoisomerases have been categorized as Type I and Type II (often referred to as "topo I" and "topo II", respectively). The clinically useful antitumor agents adriamycin, mitoxantrone, etoposide and m-AMSA have been reported to work by inhibiting the function of Type II topoisomerase. Camptothecin, a natural product antitumor agent, has been found to inhibit the function of Type I topoisomerase as have certain synthetic camptothecin analogs (see Wall, *et al.*, US patent 4,894,456). It is now

believed that a compound which could effectively inhibit the functions of either or both Type I and Type II would be a potent antitumor agent.

SUMMARY OF THE INVENTION

One aspect of the present invention is the genus of the compounds of formula (I),



(I)

wherein:

R^1 is hydrogen, hydroxy, fluoro, chloro, bromo, iodo, methoxy or amino;

R^2 is hydrogen, hydroxy, methoxy or amino;

R^3 is hydrogen, hydroxy, methoxy, methoxymethoxy, amino, $-OCONH_2$, [2(5H)-3,4-dihydro-3-oxyfuranone], 2-hydroxyethoxy, 2-aminoethoxy, 3-hydroxypropoxy or 3-aminopropoxy; or taken together with R^2 or R^4, methylenedioxy or ethylenedioxy;

R^4 is hydrogen, hydroxy or amino;

Z is $-CH_2-$, -O- or -NH-; and

a) X^1 is hydrogen;
X^2 is hydrogen, hydroxy, fluoro, chloro, bromo, iodo or methoxy; and
X^3 is hydrogen or hydroxy; or

b) X^2 taken together with X^3 is methylenedioxy or ethylenedioxy, and
X^1 is hydrogen

or a pharmaceutically acceptable salt thereof

provided that:

i) at least one of R^1 through R^4 is other than hydrogen;

ii) when R^1 is methoxy, R^2 is hydroxy or methoxy, R^3 is

hydrogen or methoxy and R^4 is hydrogen;

iii) when R^2 is hydroxy, methoxy or amino, R^3 is hydrogen, hydroxy or methoxy, and R^4 is hydrogen;

iv) when R^4 is hydroxy or amino, R^1 and R^3 are hydrogen and R^2 is hydroxy or amino; and.

v) when R^1 is fluoro, chloro, iodo or amino, R^2 is hydrogen, hydroxy or methoxy, R^3 is hydrogen, hydroxy or methoxy and R^4 is hydrogen.

As will be understood by those skilled in the art, pharmaceutically acceptable salts include, but are not linited to salts with inorganic acids such hydrochloride, sulfate, phosphate, diphosphate, hydrobromide and nitrate or salts with an organic acid such as malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methansulfonate, p-toluenesulfonate, palmoate, salicylate and sterate.

Another aspect of the invention is a method of inhibiting topoisomerase Types I and II in mammalian cells comprising contacting these enzymes with a topoisomerase inhibiting amount of a compound of formula (I), and a method of treating a tumor in a mammal comprising administering to a mammal bearing a tumor, an effective antitumor amount of a compound of formula (I). A further aspect comprises pharmaceutical formulations containing a compound of formula (I) as an active ingredient. Novel chemical intermediates used in the synthesis, as taught herein, of the compounds of formula (I) are also within the scope of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

Particular compounds of formula (I) are those wherein:

A X^2 taken together with X^3 is methylenedioxy

B. Z is $-CH_2-$

C. Z is -O-

D. Z is -NH-

E. X^2 is hydroxy, chloro or methoxy; and

X^3 is hydrogen or hydroxy,

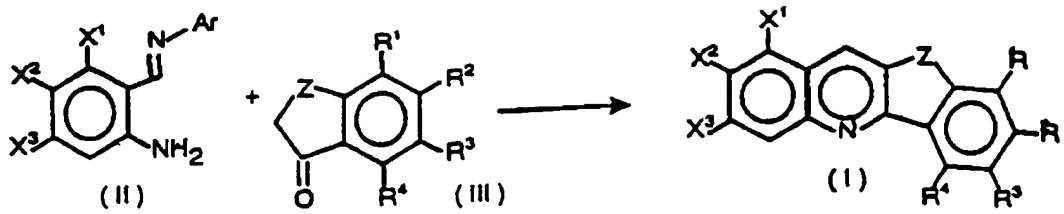
including combinations of the above, *e.g.*, (A and B), (A and C), (B and E), (A and D), (D and E) and (C and E).

Specific compounds of formula (I) are:

Compound / Example Number	Compound Name
1.	8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline
2.	7,8,9-trimethoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline
3.	7,8-dimethoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline
4.	7-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline
5.	7,9-dimethoxy-8-hydroxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline
6.	6,7-(1,4-dioxano)-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline
7.	7,8-(1,4-dioxano)-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline
8a.	7-methoxymethoxy-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline
8b.	7-hydroxy-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline
9.	7-(2-aminoethoxy)-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline
10.	7-(2-hydroxyethoxy)-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline
11.	8-methoxy-9-hydroxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline
12.	(+/-)7-[2(5H)-3,4-dihydro-3-oxyfuranone]-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline

Example / Compound Number	Compound Name
13.	7-n-methylcarbamoyl-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline
14b.	7-methoxy-8-hydroxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline
15b.	7,8-dihydroxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline
16b.	8-hydroxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline
17	2,3-dimethoxy-11H-indeno-8-chloro-[1,2-b]quinoline
18	2,3-dimethoxy-11H-indeno-[1,2-b]quinolin-8-ol
19	2,3-dimethoxy-11H-indeno-8-methoxy-[1,2-b]quinolin-7-ol
20	2,3-dihydroxy-11H-indeno-[1,2-b]quinolin-8-ol
21	2-hydroxy-3-methoxy-11H-indeno-[1,2-b]quinolin-8-ol
22	2-methoxy-3-hydroxy-11H-indeno-[1,2-b]quinolin-8-ol
23	2-methoxy-11H-indeno-[1,2-b]quinolin-8-ol
24	2-hydroxy-11H-indeno-[1,2-b]quinolin-8-ol
25	7,8-dimethoxybenzofuro[3,2-b]quinolin-2-ol
26	7,8-dimethoxybenzofuro-1,3-dioxolo[3,2-b]quinoline
27	8-methoxybenzofuro-1,3-dioxolo[3,2-b]quinoline
28	6,8-dihydroxybenzofuro-1,3-dioxolo[3,2-b]quinoline
29	6,8-dihydroxybenzofuro[3,2-b]quinolin-2-ol

As shown in Scheme (I):



SCHEME I

a compound of formula (II), wherein X^1 through X^3 are as defined for formula (I), and Ar is a C_{6-12}, one or two ring, substituted or unsubstituted, aromatic group (*e.g.*, phenyl or 4-toluyl), may be reacted with a compound of formula (III), wherein R^1 through R^4 and Z are as defined for formula (I), to yield a corresponding compound of formula (I). This reaction may be conveniently carried out in a polar solvent system, for example, water, (C_{1-4}) alkanol, (C_{2-4}) alkylene diol or mixture thereof (*e.g.*, water / ethanol) in the presence of a compatible strong mineral acid or alkali metal hydroxide base (*e.g.*, sulfuric acid or sodium hydroxide) at a temperature in the range of from about 50°C to about 150°C. See C. Cheng,"Friedländer Synthesis of Quinolines," *Organic Reactions*, 28, 37-201, John Wiley, New York (1982).

A compound of formula (I) prepared by this reaction scheme may be purified by conventional methods of the art, *e.g.*, chromatography, distillation or crystallization.

Where R^1, R^2, R^3 or R^4 of a compound of formula (III); or X^2 or X^3 of a compound of formula (II) are base sensitive hydroxy, it is preferable to protect these functionalities by converting them into protected derivatives, herein referred to collectively as "protected hydroxy functions" or "protected hydroxy." For example, hydroxy may be converted to an ether, *e.g.*, alkoxyalkyl ethers or benzyl ethers, by methods known in the art, such as those taught in T. Green, *Protective Groups in Organic Chemistry*, Chap. 3, John Wiley, New York (1981). Protected hydroxy functions are stable to bases, compatible with basic catalysis conditions if used in

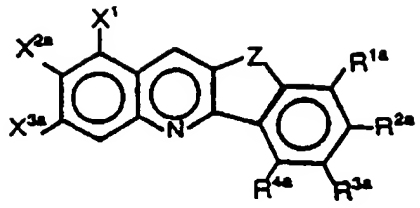
the reaction of Scheme (I) and can conveniently be reconverted to the corresponding hydroxys by conventional techniques, such as those taught by T. Green, *supra, e.g.,* by treatment with acid, following completion of the reaction of Scheme (I).

Likewise, where R^1 and/or R^3 are the acid or base sensitive amino, it is preferable to the protect the amino function by converting it into a protected amino derivative (herein, "protected amino"), *e.g.,* an amide or a carbamate, by methods known in the art, such as those methods taught in T. Green, *supra*, Chap. 7. Protected amino functions are selected to be compatible with acidic or basic catalysis conditions used for the reaction of Scheme (I) and can conveniently be reconverted to amino by conventional techniques, such as those taught by T. Green, *supra, e.g.,* hydrogenation using a palladium on carbon catalysis, after completion of the reaction of Scheme (I).

Compounds of formula (I) may be convered to other compounds of formula (I). For example a compound of formula (I) bearing a methoxymethoxy function can be converted to a corresponding compound of formula (I) bearing an hydroxy function by treatment with a (C_{1-4}) alkanoic acid, *e.g.,* refluxing in acetic acid.

The compounds of formulas (II) and (III) are either available commercially or may be prepared by methods of the art. For example, the compounds of formula (II) may be prepared by the methods taught by C. Cheng, *supra,* and the compounds of formula (III) may be prepared by the method taught by A. I. Vogel, *Practical Organic Chemistry*, 4th Ed., 773, Longmans, London (1978).

The intermediate compounds of formula (IA) having at least one protected function



(IA)

wherein:

R^{1a} is hydrogen, protected hydroxy, fluoro, chloro, bromo, iodo, methoxy or protected amino;

R^{2a} is hydrogen, protected hydroxy, methoxy or protected amino;

R^{3a} is hydrogen, protected hydroxy, methoxy, protected amino, $-OCONH_2$, [2(5H)-3,4-dihydro-3-oxyfuranone], 2-hydroxyethoxy, 2-amino-ethoxy, 3-hydroxypropoxy or, taken together with R^{2a} or R^{4a}, methylenedioxy or ethylenedioxy;

R^{4a} is hydrogen, protected hydroxy or protected amino;

Z is $-CH_2-$, -O- or -NH-; and

a) X^1 is hydrogen;
X^{2a} is hydrogen, protected hydroxy, F, Cl, Br, I or methoxy;
X^{3a} is hydrogen or protected hydroxy; or

b) X^{2a} taken together with X^{3a} is methylenedioxy or ethylenedioxy, and
X^1 and is hydrogen

or a pharmaceutically acceptable salt thereof

provided that:

i) at least one of R^{1a} through R^{4a} is other than hydrogen;

ii) when R^{1a} is methoxy, R^{2a} is protected hydroxy or methoxy and R^{3a} is methoxy or hydrogen;

iii) when R^{2a} is protected hydroxy, methoxy or protected amino, R^{3a} is hydrogen,

hydroxy or methoxy, and R^4 is hydrogen;

iv) when R^{4a} is protected hydroxy or protected amino, R^1 and R^3 are hydrogen and R^2 is

protected hydroxy or protected amino; and

v) when R^1 is fluoro, chloro, iodo or protected amino, R^2 is hydrogen, hydroxy or methoxy, R^3 is hydrogen, protected hydroxy or methoxy and R^4 is hydrogen.

are within the scope of the present invention. Particular protected hydroxy functions include alkoxy, aryloxy, alkylaryloxy, alkoxyaryloxy and alkoxyalkoxy, *e.g.*, -O-CH_2-O-CH_3, -O-$CH_2C_6H_5$ and -O-CO-C_2H_5. As used herein "alkyl" means C_{1-6} alkyl, "alkoxy" means C_{1-6} alkoxy and "aryl" means phenyl, alkyl substituted phenyl or alkoxy substituted phenyl. Particular protected amino functions are -NHalkanoyl, *e.g.*, -$NHCOCH_3$ and -$NHCOOCH_3$.

Specific compounds of formula (IA) are:

Example \ Compound Number	Compound Name
14a.	7-methoxy-8-methoxymethoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline
15a.	7,8-dimethoxymethoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline
16a.	8-methoxymethoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline.
18a.	2,3-dimethoxy-11H-indeno-8-(4-methoxybenzoxy)-[1,2-b]quinoline
19a.	2,3-dimethoxy-11H-indeno-7-(4-methoxybenzoxy)-8-methoxy-[1,2-b]quinoline
20a.	2,3-dibenzoxy-11H-indeno-8-(4-methoxybenzoxy)-[1,2-b]quinoline
21a.	2-benzoxy-3-methoxy-11H-indeno-8-(4-methoxybenzoxy)-[1,2-b]quinoline
22a.	2-methoxy-3-benzoxy-11H-indeno-8-(4-methoxybenzoxy)-[1,2-b]quinoline
23a.	2-methoxy-11H-indeno-8-(4-methoxybenzoxy)-[1,2-b]quinoline
24a.	2-benzoxy-11H-indeno-8-(4-methoxybenzoxy)-[1,2-b]quinoline
25a.	7,8-dimethoxybenzofuro-2-(4-methoxybenzyl)-[3,2-b]quinoline
28a.	6,8-dimethoxymethoxybenzofuro-1,3-dioxolo[3,2-b]quinoline
29a.	6,8-dibenzoxybenzofuro-2-(4-methoxybenzoxy)-[3,2-b]quinoline

The data from the Cleavable Complex Assay in Table A, below, shows the relative topoisomerase Types I and II inhibitory activity of the compounds of Formula (I). This assay performed according to the method described in Hsiang, Y. et al., J. Biol. Chem., 260:14873-14878 (1985), correlates well with in vivo anti-tumor activity of topoisomerase inhibitors in animal models of cancer, *e.g.*, camptothecin and its analogs. See Hsiang et al., Cancer

Research, 49:4385-4389 (1989) and Jaxel et al., Cancer Research, 49:1465-1469 (1989). In this assay compounds exhibiting no observable inhibitory activity at concentrations of greater than about 60 µg/mL (indicated by "-" in table A, below) are considered to be of no practical value as topoisomerase inhibitors. Those compounds which exhibit observable activity in the concentration range of from about 12 µg/mL to about 60 µg/mL ("+" in table A) are considered weakly active to moderately active, while those active in the range of from about 3 µg/mL to about 12 µg/mL ("++" in table A) are moderately active. Compounds active at concentrations less than 3 µg/mL ("+++" in table A) are considered to be strongly active topoisomerase inhibitors. Certain compounds of formula (I), *e.g.*, compounds 1 and 10, inhibit both Type I and Type II topoisomerase.

TABLE A

Topoisomerase Inhibitory Activity of

Compounds of Formula (I) in the Cleavable Complex Assay

Compound Number	Topo I	Topo II
1	+++	++
2	+	-
3	+++	+++
4	-	+
5	++	++
6	-	++
7	-	+++
8a	++	-
8b	+++	++
9	-	+++

Compound Number	Topo I	Topo II
10	+++	+
11	-	+++
12	+	-
13	-	+++
14b	+++	+++
15b	+++	+++
16b	-	+
17	+++	-
18	+++	++
19	++	-
20	+++	+++
21	+++	+++
22	+++	+++
23	-	+
24	++	++
25	+++	++
26	++	++
27	+++	++
28	-	+
29	++	++

"-" Indicates no activity of practical value.
"+" Indicates positive activity, and the number of "+" signs indicates relative activity (see description of this assay, above).

In view of such activity, the compounds of formula (I) are active against a wide spectrum of mammalian (including human) tumors and cancerous growths such as cancers of the oral cavity and pharynx (lip, tongue, mouth, pharynx), esophagus, stomach, small intestine, large intestine, rectum, liver and biliary passages, pancreas, larynx, lung, bone, connective tissue, skin, colon, breast, cervix uteri, corpus endometrium, ovary, prostate, testis, bladder, kidney and other urinary tissues, eye, brain and central nervous system, thyroid and other

endocrine gland, leukemias (lymphocytic, granulocytic, monocytic), Hodgkin's disease, non-Hodgkin's lymphomas, multiple myeloma, etc. Herein the terms "tumor", "cancer" and "cancerous growths" are used synonymously.

The amount of compound of formula (I) required to be effective as an antitumor agent will, of course, vary with the individual mammal being treated and is ultimately at the discretion of the medical or veterinary practitioner. The factors to be considered include the condition being treated, the route of administration, the nature of the formulation, the mammal's body weight, surface area, age and general condition, and the particular compound to be administered. However, a suitable effective antitumor dose is in the range of about 0.1 to about 200 mg/kg body weight per day, preferably in the range of about 1 to about 100 mg/kg per day. The total daily dose may be given as a single dose, multiple doses, e.g., two to six times per day, or by intravenous infusion for a selected duration. Dosages above or below the range cited above are within the scope of the present invention and may be administered to the individual patient if desired and necessary.

For example, for a 75 kg mammal, a dose range would be about 75 to about 7500 mg per day, and a typical dose would be about 800 mg per day. If discrete multiple doses are indicated, treatment might typically be 200 mg of a compound of formula (I) given 4 times per day.

Formulations of the present invention, for medical use, comprise an active compound, *i.e.*, a compound of formula (I), together with an acceptable carrier therefor and optionally other therapeutically active ingredients. The carrier must be pharmaceutically acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The present invention, therefore, further provides a pharmaceutical formulation comprising a compound of formula (I) together with a pharmaceutically acceptable carrier thereof.

The formulations include those suitable for oral, rectal or parenteral (including subcutaneous, intramuscular and intravenous) administration. Preferred are those suitable for oral or parenteral administration.

The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active compound into association with a carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active compound into association with a liquid carrier or a finely divided solid carrier and then, if necessary, shaping the product into desired unit dosage form.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets or lozenges, each containing a predetermined amount of the active compound; as a powder or granules; or a suspension or solution in an aqueous liquid or non-aqueous liquid, *e.g.*, a syrup, an elixir, an emulsion or a draught.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active compound in a free-flowing form, *e.g.*, a powder or granules, optionally mixed with accessory ingredients, *e.g.*, binders, lubricants, inert diluents, surface active or dispersing agents. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered active compound with any suitable carrier.

A syrup or suspension may be made by adding the active compound to a concentrated, aqueous solution of a sugar, *e.g.*, sucrose, to which may also be added any accessory ingredients. Such accessory ingredient(s) may include flavoring, an agent to retard crystallization of the sugar or an agent to increase the solubility of any other ingredient, *e.g.*, as a polyhydric alcohol, for example, glycerol or sorbitol.

Formulations for rectal or vaginal administration may be presented as a suppository with a conventional carrier, *e.g.*, cocoa butter or Witepsol S55 (trademark of Dynamite Nobel Chemical, Germany, for a suppository base).

Formulations suitable for parenteral administration conveniently comprise a sterile aqueous preparation of the active compound which is preferably isotonic with the blood of the recipient. Such formulations suitably comprise a solution or suspension of a pharmaceutically and pharmacologically acceptable acid addition salt of a compound of the formula (I) that is isotonic with the blood of the recipient. Thus, such formulations may conveniently contain distilled water, 5% dextrose in distilled water or saline and a pharmaceutically and pharmacologically acceptable acid addition salt of a compound of the formula (I) that has an appropriate solubility in these solvents, for example the hydrochloride, isethionate and methanesulfonate salts, preferably the latter. Useful formulations also comprise concentrated solutions or solids containing the compound of formula (I) which upon dilution with an appropriate solvent give a solution suitable for parental administration above.

In addition to the aforementioned ingredients, the formulations of this invention may further include one or more optional accessory ingredient(s) utilized in the art of pharmaceutical formulations, *e.g.*, diluents, buffers, flavoring agents, binders, surface active agents, thickeners, lubricants, suspending agents, preservatives (including antioxidants) and the like.

EXAMPLES

The following examples illustrate aspects of this invention but should not be construed as limitations. The symbols and conventions used in these examples are consistent with those used in the contemporary chemical literature, for example, the *Journal of the American Chemical Society.*

Example 1

8-Methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline (Compound 1)

To 5-methoxyindan-1-one (350 mg, 2 mmol) is added 6[[(4-methylphenyl)-imino]methyl]-1,3-benzodioxol-5-amine (512 mg, 1 mmol) in ethanol (4 mL) and 2N sodium hydroxide (1 mL). The reaction mixture is heated at reflux (about 100°C) for 16 hrs. Upon cooling the reaction product is dissolved in methylene chloride (200 mL) and extracted with a saturated sodium chloride solution (200 mL). The organic layer is dried with a rotatory evaporator. The resulting residue is chromatographed on silica gel with 2:3 ethyl acetate / hexanes to yield 8-Methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline (393 mg, 67.4% of theory).

1H-300 NMR (CDCl3): δ 3.93 (s, 3H); 3.97 (s, 2H); 6.14 (s, 2H); 7.16 - 7.05 (m, 3H); 7.50 (s, 1H); 7.99 (s, 1H); 8.15 (d, 1H).

High Resolution Exact Mass: (for $C_{18}H_{13}NO_3$)

Calc. = 292.0974

Found = 292.0983

Example 2

7,8,9-Trimethoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline (Compound 2)

Using the procedure of Example 1, 4,5,6-trimethoxyindan-1-one (1.10 mg, 4.8 mmol) is reacted with 6[[(4-methylphenyl)imino]methyl]-1,3-benzodioxol-5-amine (1.22 g, 4.8 mmol) to yields 7,8,9-trimethoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline (0.84 mg, 49.9% of theory).

^{1}H-300 NMR ($CDCl_3$): δ 3.94 (s, 2H); 3.99 (s, 3H); 4.06 (s, 3H); 4.09 (s, 3H); 6.15 (s, 3H); 7.12 (s, 1H); 7.56 (s, 1H); 7.56 (s, 1H); 8.03 (s, 1H).

Elemental analysis: (for $C_{20}H_{17}NO_5$)

	%C	%H	%N
Found:	68.22	4.87	4.09
Calculated:	68.37	4.88	3.99

Example 3

7,8-Dimethoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline (Compound 3)

Using the procedure of Example 1, 5,6-dimethoxyindan-1-one (192 mg, 1 mmol) is reacted with 6[[(4-methylphenyl)imino]methyl]-1,3-benzodioxol-5-amine (255 mg, 1 mmol) to yields 7,8-dimethoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline (260 mg, 81% of theory).

^{1}H-300 NMR ($CDCl_3$): δ 3.92 (s, 2H); 4.02 (s, 3H); 4.09 (s, 3H); 6.14 (s, 2H); 7.11 (s, 1H); 7.14 (s, 1H); 7.51 (s, 1H); 7.73 (s, 1H); 8.00 (s, 1H).

High Resolution Exact Mass: (for $C_{19}H_{15}NO_4$)

Calc. = 322.1079

Found = 322.1094

Example 4

7-Methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline (Compound 4)

Using the procedure of Example 1, 6-methoxyindan-1-one (162 mg, 1 mmol) is reacted with 6[[(4-methylphenyl)imino]methyl]-1,3-benzodioxol-5-amine (255 mg, 1 mmol) to yields 7-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline (130 mg, 44.6% of theory).

^{1}H-300 NMR ($CDCl_3$): δ 3.94 (s, 2H); 4.00 (s, 3H); 6.15 (s, 2H); 7.07 (dd, J = 8.3, 2.6 hz, 1H); 7.13 (s, 1H); 7.51 (d, J = 8.3 hz, 1H); 7.54 (s, 1H); 7.76 (d, J = 2.44 hz, 1H); 8.05 (s, 1H).

High Resolution Exact Mass: (for $C_{18}H_{13}NO_3$)

Calc. = 292.0974

Found = 292.0998

Example 5

7,9-Dimethoxy-8-hydroxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline (Compound 5)

(A) Using the procedure of Example 1, 4,6-dimethoxy-5-methoxymethoxyindan-1-one (100 mg, 0.4 mmol) is reacted with 6[[(4-methylphenyl)imino]methyl]-1,3-benzodioxol-5-amine (101 mg, 0.4 mmol) to yields 7,9-dimethoxy-8-methoxymethoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline (120 mg, 79% of theory). This material was used directly in part (B).

(B) The product of part (A) (120 mg, 0.31 mmol), tetrahydrofuran (5 mL) and 2N HCl (5 mL) are heated at reflux (about 80°C) for about 16 Hrs. After cooling to room temperature, the reaction mixture is washed with about 50 mL saturated aqueous sodium bicarbonate and the organic layer separated and dried over anhydrous magnesium sulfate. The anhydrous magnesium sulfate is removed by filtration and the organic solution is concentrated on a rotory evaporator to a thick residue. This residue is chromatographed (silica gel eluded with 70% ethyl acetate/ 30% hexane) to yield 7,9-Dimethoxy-8-hydroxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline (41 mg, 39% of theory).

^{1}H-300 NMR ($CDCl_3$): δ 3.98 (s, 2H); 4.09 (s, 3H); 4.11 (s, 3H); 5.91 (s, 1H); 6.14 (s, 2H); 7.12 (s, 1H); 7.50 (s, 1H); 7.55 (s, 1H); 8.02 (s, 1H).

High Resolution Exact Mass: (for $C_{19}H_{13}NO_4$)

Calc. = 388.1029

Found = 388.1034

Example 6

6,7-(1,4-Dioxano)-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline (Compound 6)

Using the procedure of Example 1, 6,7-(1,4-dioxano)indan-1-one (115 mg, 0.61 mmol) is reacted with 6[[(4-methylphenyl)imino]methyl]-1,3-benzodioxol-5-amine (154 mg, 0.61 mmol) to yields 6,7-(1,4-dioxano)-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline (89 mg, 46% of theory).

^{1}H-300 NMR ($CDCl_3$): δ 3.95 (s, 2H); 4.42 (m, 2H); 4.63 (m, 2H); 6.14 (s, 2H); 7.01 (d, 1H); 7.08 (d, 1H); 7.09 (s, 1H); 7.59 (s, 1H); 8.02 (s, 1H).

High Resolution Exact Mass: (for $C_{19}H_{13}NO_4$)

Calc. = 320.0923

Found = 320.0947

Example 7

7,8(1,4-Dioxano)-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline (Compound 7

Using the procedure of Example 1, 5,6-(1,4-dioxano)indan-1-one (191 mg, 1 mmol) is reacted with 6[[(4-methylphenyl)imino]methyl]-1,3-benzodioxol-5-amine (254 mg, 1 mmol) to yields 7,8-(1,4-dioxano)-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline (205 mg, 64% of theory).

^{1}H-300 NMR ($CDCl_3$): δ 3.89 (s, 2H); 4.36 (s, 4H); 6.14 (s, 2H); 7.09 (s, 2H); 7.50 (s, 1H); 7.73 (s, 1H); 7.98 (s, 1H).

High Resolution Exact Mass: (for $C_{19}H_{13}NO_4$)

Calc. = 320.0923

Found = 320.0916

Example 8

7-Hydroxy-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline (Compound 8)

(A) Using the procedure of Example 1, 5-methoxy-6-methoxymethoxyindan-1-one (452 mg, 2.03 mmol) is reacted with 6[[(4-methylphenyl)imino]methyl]-1,3-benzodioxol-5-amine (517 mg, 2.03 mmol) to yields 7-methoxymethoxy-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline. This material is used

directly in part (B) without further isolation or purification except for the few milligrams need for NMR and mass spectral studies.
^{1}H-300 NMR (acetone ^{6}D): δ 3.76 (s, 3H); 4.14 (s, 2H); 4.16 (s, 3H); 5.54 (s, 2H); 6.40 (s, 2H); 7.44 (s, 1H); 7.51 (s, 1H); 7.58 (s, 1H); 8.30 (s, 1H); 8.33 (s, 1H).
Nominal Mass:
m + 1 = 352

(B) The product of part (A), tetrahydrofuran (10 mL) and 2N HCl (10 mL) are heated at reflux (about 80°C) for about 16 Hrs. After cooling to room temperature, the reation mixture is washed with about 50 mL saturated aqueous sodium bicarbonate and the organic layer separated and dried over anhydrous magnesium sulfate. The anhydrous magnesium sulfate is removed by filtration and the organic solution is concentrated on a rotory evaporator to a thick residue. This residue is chromatographed (silica gel eluded with 70% ethyl acetate/ 30% hexane) to yield 7-hydroxy-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline (41 mg, 39% of theory).
^{1}H-300 NMR (d^6 DMSO): δ 3.97 (s, 5H); 6.29 (s, 2H); 7.32 (s, 1H); 7.43 (s, 1H); 7.48 (s, 1H); 7.49 (s, 1H); 8.24 (s, 1H); 9.36 (s, 1H).
High Resolution Exact Mass: (for $C_{18}H_{13}NO_4$)
Calc. = 308.0923
Found = 308.0933

Example 9

7-(2-Aminopropoxy)-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline (Compound 9)

(A) Using the procedure of Example 1, 6-(3-N-phthalimidopropoxy)-8-methoxyindan-1-one (366 mg, 1 mmol) is reacted with 6[[(4-methylphenyl)-imino]methyl]-1,3-benzodioxol-5-amine (255 mg, 1 mmol) to yields 7-(3-N-phthalimidopropoxy)-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline (268 mg, 54.2% of theory).

^{1}H-300 NMR ($CDCl_3$): δ 2.35 (m, 2H); 3.83 (s, 3H); 3.89 (s, 2H); 4.01 (t, J = 6.83 hz, 2H); 4.31 (t, J = 6.23 hz, 2H); 6.14 (s, 2H); 7.07 (s, 1H); 7.10 (s, 1H); 7.49 (s, 1H); 7.69 (s, 1H); 7.73 (d, J = 5.37 hz, 1H); 7.75 (d, J = 5.62 hz, 1H); 7.87 (d, J = 5.62 hz, 1H); 7.89 (d, J = 5.37 hz, 1H); 7.98 (s, 1H).

Nominal Mass:

m + 1 = 495

(B) The product of part (A) (50 mg, 0.1 mmol), andydrous ethanol (5 mL) and anhydrous hydrazine (0.2 mL) are heated at about 50°C under nitrogen for about 16 Hrs. The reaction is then cooled to about 0°C, filtered and the residue washed with anhydrous ethanol (at about 0°C). The residue is triturated with minimal methylene chloride. To the resulting methylene chloride solution is added hexane until a solid is precipitated. This solid is recoved by filtration and dried, *in vacuo*, at ambient temperature to yield 7-(2-aminopropoxy)-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline (28.9 mg, 79.4% of theory).

^{1}H-300 NMR ($CDCL_3$): δ 2.10 (m, 2H); 3.01 (t, J = 6.72 hz, 2H); 3.91 (s, 2H); 3.99 (s, 3H); 4.32 (t, J = 6.35 hz, 2H); 6.14 (s, 2H); 7.11 (s, 1H); 7.13 (s, 1H); 7.50 (s, 1H); 7.75 (s, 1H); 7.99 (s, 1H).

High Resolution Exact Mass: (for $C_{21}H_{20}N_2O_4$)

Calc. = 365.1501

Found = 365.1486

Example 10

7-(2-Hydroxyethoxy)-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline (Compound 10)

Using the procedure of Example 1, 5-methoxy-6-(2-hydroxyethoxy)indan-1-one (222 mg, 1 mmol) is reacted with 6[[(4-methylphenyl)imino]methyl]-1,3-benzodioxol-5-amine (255 mg, 1 mmol) to yields 7-(2-hydroxyethoxy)-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline (239 mg, 68% of theory).

^{1}H-300 NMR ($CDCl_3$): δ 2.61 (t, J=5.85 hz, 1H); 3.93 (s, 2H); 4.00 (s, 3H); 4.05 (m, 2H); 4.34 (t, J=4.64 hz, 2H); 6.14 (s, 2H); 7.11 (s, 1H); 7.15 (s, 1H); 7.50 (s, 1H); 7.78 (s, 1H); 8.00 (s, 1H).

High Resolution Exact Mass: (for $C_{20}H_{17}NO_5$)

Calc. = 352.1185

Found = 352.1195

Example 11

8-Methoxy-9-hydroxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline (Compound 11)

(A) Using the procedure of Example 1, 4-benzoxy-5-methoxyindan-1-one (mg, 2 mmol) is reacted with 6[[(4-methylphenyl)imino]methyl]-1,3-benzodioxol-5-amine (510 mg, 2 mmol) to yields 8-methoxy-9-hydroxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline (308 mg, 38.7% of theory) which is used as a starting material for part (B).

(B) The product of part (A) (302 mg, 0.76 mmol), anhydrous ethyl acetate (30 mL), anhydrous tetrahydrofuran (8 mL) and 10% palladium on carbon (0.35 g) are shaken in a sealed bottle containing hydrogen at 1 atm. at ambient temperature for about 2 hrs. The reaction is then filtered through a pad of diatomaceous earth filter aid. The solvent is removed by reduced pressure evaporation to yield a solid residue. This residue is dissolved in minimal methylene chloride and hexane is added to precipitate 8-methoxy-9-hydroxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline (220 mg, 94% of theory).

^{1}H-300 NMR ($CDCl_3$): δ 3.98 (s, 2H); 4.01 (s, 3H); 5.95 (s, 1H); 6.14 (s, 2H); 7.06 (d, J=8.06 hz, 1H); 7.11 (s, 1H); 7.51 (s, 1H); 7.78 (d, J=8.3 hz, 1H); 8.04 (s, 1H).

High Resolution Exact Mass: (for $C_{18}H_{13}NO_4$)

Calc. = 308.0923

Found = 308. 0945

Example 12

(+/-)7-[2(5H)-3,4-Dihydro-3-oxyfuranone]-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline (Compound 12)

Using the procedure of Example 1, 5-methoxy-6-[2(5H)-3,4-dihydro-3-oxyfuranone]indan-1-one (262 mg, 1 mmol) is reacted with 6[[(4-methyl-phenyl)imino]methyl]-1,3-benzodioxol-5-amine (255 mg, mmol) to yields (+/-)7-[2(5H)-3,4-dihydro-3-oxyfuranone]-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline (106 mg, 27% of theory).

^{1}H-300 NMR ($CDCl_3$): δ 2.61 (m, 1H); 2.86 (m, 1H); 3.93 (s, 2H); 4.00 (s, 3H); 4.41 (m, 1H); 4.61 (m, 1H); 5.19 (t, j=8.06 hz, 1H); 6.14 (s, 2H); 7.10 (s, 1H); 7.17 (s, 1H); 7.48 (s, 1H); 7.85 (s, 1H); 8.00 (s, 1H).

High Resolution Exact Mass: (for $C_{22}H_{17}NO_7$)

Calc. = 392.1134

Found = 392.1151

Example 13

7-n-Methylcarbamoyl-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline (Compound 13)

Compound 8, prepared in Example 8, (308 mg, 1 mmol), anhydrous methylene chloride (5 mL), 4-dimethylamino pyridine (489 mg, 4 mmol) and methyl isocyanate (171 mg, 0.18 mmol) are stirred at about 0°C under a dry nitrogen atmosphere for about an hour. The reaction is allowed to cool to ambient temperature. Stirring is continued for about 16 hrs. while maintaining the nitrogen atmosphere. The solvent is then removed by reduced pressure evaporation to give a solid residue. This residue is chromatographed (silica gel eluded with ethyl acetate) to yield 7-n-Methylcarbamoyl-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline.

^{1}H-300 NMR (DMSO D^6): δ 2.26 (s, 3H); 3.62 (s, 5H); 5.94 (s, 2H); 6.97 (s, 1H); 7.09 (s, 1H); 7.14 (s, 1H); 7.15 (s, 1H); 7.89 (s, 1H); 9.00 (s, 1H).

Example 14

7-Methoxy-8-methoxymethoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline (Compound 14a) and 7-Methoxy-8-hydroxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline (Compound 14b)

(A) Using the procedure of Example 1, 5-methoxy-6-methoxymethoxyindan-1-one (1000 mg, 4.5 mmol) is reacted with 6[[(4-methylphenyl)imino]methyl]-1,3-benzodioxol-5-amine (1144 mg, 4.5 mmol) to yields 7-Methoxy-8-methoxymethoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline (400 mg, 25% of theory).

^{1}H-300 NMR ($CDCl_3$): δ 3.53 (s, 3H); 3.84 (s, 2H); 4.01 (s, 3H); 5.29 (s, 2H); 6.07 (s, 2H); 7.04 (s, 1H); 7.35 (s, 1H); 7.44 (s, 1H); 7.69 (s, 1H); 7.94 (s, 1H).

Nominal Mass:

m/e = 351

(B) The product of part (A) (80 mg 0.23 mmol) is stirred with trifluoroacetic acid (0.43 mL, 5.6 mmol) and methylene chloride (1 mL) at ambient temperature for about 16 hours. The reaction is then quenched with saturated sodium bicarbonate solution (about 10 mL), and extracted with ethyl acetate (3 x 10 mL). The combined organic phases are dried over anhydrous sodium sulfate, filtered and stripped of solvent by reduced pressure evaporation to yield 7-methoxy-8-hydroxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline (56 mg, 65% of theory)

^{1}H-300 NMR ($CDCL_3$): δ 3.84 (s, 2H); 4.01 (s, 3H); 6.08 (s, 2H); 6.21 (brs, 1H); 7.05 (s, 1H); 7.11 (s, 1H); 7.45 (s, 1H); 7.67 (s, 1H); 7.93 (s, 1H).

Nominal Mass:

m/e = 307

Elemental analysis: (for $C_{18}N_{13}N_1O_4$)

	%C	%H	%N
Found:	68.42	4.88	4.04
Calculated:	68.37	4.88	3.99

Example 15

7,8-Dimethoxymethoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline (Compound 15a) and 7,8-dihydroxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline (Compound 15b)

(A) Using the procedure of Example 1, 5,6-dimethoxymethoxyindan-1-one (504 mg, 2 mmol) is reacted with 6[[(4-methylphenyl)imino]methyl]-1,3-benzodioxol-5-amine (508 mg, 2 mmol) to yields 7,8-dimethoxymethoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline (307 mg, 40% of theory).

^{1}H-300 NMR ($CDCl_3$): δ 3.53 (s, 3H); 3.54 (s, 3H); 3.85 (s, 2H); 5.30 (s, 2H); 5.35 (s, 2H); 6.07 (s, 2H); 7.03 (s, 1H); 7.35 (s, 1H); 7.43 (s, 1H); 7.92 (s, 2H).

Nominal Mass:

m/e = 381

(B) The product of part (A) (307 mg, 0.8 mmol) was hydrolyzed by the procedure of Example 14 (B) using proportionate amounts of the other reagents to yield 7,8-dihydroxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline (6.7 mg, 3% of theory).

^{1}H-300 NMR (d^6 DMSO): δ 3.81 (s, 2H); 6.18 (s, 2H); 7.00 (s, 1H); 7.34 (s, 1H); 7.36 (s, 1H); 7.39 (s, 1H); 8.14 (s, 1H); 9.31 (brs, 1H); 9.50 (brs, 1H).

Nominal Mass:

m/e = 293

Example 16

8-Methoxymethoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline (Compound 16a) and 8-hydroxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline (Compound 16b)

(A) Using the procedure of Example 1, 5-methoxymethoxyindan-1-one (327 mg, 1.7 mmol) is reacted with 6[[(4-methylphenyl)imino]methyl]-1,3-benzodioxol-5-amine (432 mg, 1.7 mmol) to yields 8-methoxymethoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline (86.3 mg, 15% of theory).

^{1}H-300 NMR ($CDCl_3$): δ 3.49 (s, 3H); 3.89 (s, 2H); 5.23 (s, 2H); 6.06 (s, 2H); 7.02 (s, 1H); 7.11 (d, J=8.5 hz, 1H); 7.22 (s, 1H); 7.43 (s, 1H); 7.92 (s, 1H); 7.06 (d, j=8.5 Hz, 1H).

Nominal Mass:

m/e = 321

(B) The product of part (A) (25 mg, 0.8 μmol) was hydrolyzed by the procedure of Example 14 (B) using proportionate amounts of the other reagents to yield 8-hydroxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline (5.5 mg, 25% of theory).

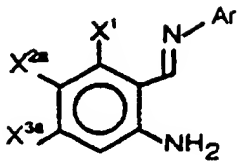
^{1}H-300 NMR (d^6 DMSO): δ 3.91 (s, 2H); 6.17 (s, 2H); 6.85 (d, j=8.0 Hz, 1H); 7.00 (s, 1H); 7.32 (s, 1H); 7.35 (s, 1H); 7.82 (d, j=8.0 Hz, 1H); 8.13 (s, 1H).

Nominal Mass:

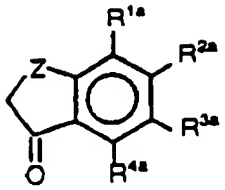
m/e = 277

Examples 17 - 29

The starting materials for Examples 17 - 29 are the compounds of formula (IIA) and formula (IIIA) where in X^1, X^{2a}, X^{3a}, and R^{1a} - R^{4a} are as defined for formula (IA)



(IIA)



(IIIA)

Example 17

2,3-Dimethoxy-11H-indeno-8-chloro-[1,2-b]quinoline (Compound 17)

This compound is prepared by the procedure of Example 1 except that an equivalent amount of the compound of formula (IIIA), wherein Z is CH_2; R^{2a} and R^{3a} are methoxy; and R^{1a} and R^{4a} are hydrogen, is used in place of 5-methoxyindan-1-one and an equivalent amount of the compound of formula (IIA) wherein X^{2a} is chloro, and X^1 and X^3 are hydrogen is used in place of 6[[(4-methylphenyl)imino]methyl]-1,3-benzodioxol-5-amine to yield 2,3-dimethoxy-11H-indeno-8-chloro-[1,2-b]quinoline (24 % of theory).

^{1}H-300 NMR ($CDCl_3$):δ 3.92 (s, 2H); 3.96 (s, 3H); 4.02 (s, 3H); 7.08 (s, 1H); 7.57 (dd, J=2.2, 9.04 hz 1H); 7.69 (s, 1H); 7.75 (d, J=2.2hz 1H); 7.99 (s, 1H); 8.04 (d, J=9.04 1H).

Nominal Mass:

m/e = 311

Example 18

2,3-Dimethoxy-11H-indeno-[1,2-b]quinolin-8-ol (Compound 18)

(A) The same procedure as Example 5 (A) is used except that an equivalent amount of the compound of formula (IIIA), wherein Z is CH_2; R^{2a} and R^{3a} are methoxy; and R^{1a} and R^{4a} are hydrogen, is used in place of 4,6-dimethoxy-5-methoxymethoxyindan-1-one and an equivalent amount of the compound of formula (IIA) wherein X^{2a} is 4-methoxybenzoxy, and X^1 and X^3 are hydrogen is used in place of 6[[(4-methylphenyl)imino]methyl]-1,3-benzodioxol-5-amine

to yield 2,3-dimethoxy-11H-indeno-8-(4-methoxybenzoxy)-[1,2-b]quinoline. This material was used directly in part (B).

Nominal Mass:

m/e = 413

(B) The procedure of Example 14 (B) is used to remove the hydroxy protecting group, *i.e.*, 4-methoxybenzyl, from the product of part (A) above and to yield 2,3-dimethoxy-11H-indeno-[1,2-b]quinolin-8-ol (88% of theory).

^{1}H-300 NMR (d^6 DMSO):δ 3.85 (s, 3H); 3.89 (s, 3H); 3.92 (s, 2H); 7.14 (d, J=2.69 hz, 1H); 7.23 (dd, J=2.69, 9.03 hz,1H); 7.27 (s, 1H); 7.52 (s, 1H); 7.87 (d, J=9.03 hz, 1H); 8.12 (s, 1H)

Elemental analysis: (for $C_{18}H_{15}NO_3$)

	%C	%H	%N
Found:	73.48	5.17	4.77
Calculated:	75.70	5.16	4.78

Example 19

2,3-Dimethoxy-11H-indeno-8-methoxy-[1,2-b]quinolin-7-ol (Compound 19)

(A) The same procedure as Example 5 (A) except is used that an equivalent amount of the compound of formula (IIIA), wherein Z is CH_2; R^{2a} and R^{3a} are methoxy; and R^{1a} and R^{4a} are hydrogen, is used in place of 4,6-dimethoxy-5-methoxymethoxyindan-1-one and an equivalent amount of the compound of formula (IIA), wherein X^1 is hydrogen, X^{2a} is methoxy, and X^3 is 4-methoxybenzoxy, is used in place of 6[[(4-methylphenyl)imino]methyl]-1,3-benzodioxol-5-amine to yield 2,3-dimethoxy-11H-indeno-7-(4-methoxybenzoxy)-8-methoxy-[1,2-b]quinoline (mp, 216-218°C). This material was used directly in part (B).

FAB m + 1 =444

(B) The procedure of Example 14 (B) is used to remove the hydroxy protecting group, *i.e.*, 4-methoxybenzyl, from the product of part (A) above and to yield 2,3-dimethoxy-11H-indeno-8-methoxy-[1,2-b]quinolin-7-ol (19% of theory).

^{1}H-300 NMR ($CDCl_3$):δ 3.87 (s, 2H); 3.96 (s, 3H); 4.01 (s, 3H); 4.02 (s, 3H); 7.05 (d, J=6.4 hz,2H); 7.61 (s, 1H); 7.72 (s, 1H); 7.95 (s,1H)

Nominal Mass:

m/e = 323

Example 20

2,3-Dihydroxy-11H-indeno-[1,2-b]quinolin-8-ol (Compound 20)

(A) The same procedure as Example 5 (A) is used except that an equivalent amount of the compound of formula (IIIA), wherein Z is CH_2; R^{2a} and R^{3a} are benzy; and R^{1a} and R^{4a} are hydrogen, is used in place of 4,6-dimethoxy-5-methoxymethoxyindan-1-one and an equivalent amount of the compound of formula (IIA), wherein X^1 and X^3 are hydrogen and X^{2a} is 4-methoxybenzoxy, is used in place of 6[[(4-methylphenyl)imino]methyl]-1,3-benzodioxol-5-amine to yield 2,3-dibenzoxy-11H-indeno-8-(4-methoxybenzoxy)-[1,2-b]quinoline. This material was used directly in part (B).

Nominal Mass:

m/e = 473

(B) The procedure of Example 14 (B) is used to remove the hydroxy protecting groups, *i.e.*, 4-methoxybenzyl and benzyl, from the product of part (A) above and to yield 2,3-dihydroxy-11H-indeno-[1,2-b]quinolin-8-ol (67% of theory).

^{1}H-300 NMR (d^6DMSO + D_2O): § 3.96 (r, 2H); 7.16 (s, 1H); 7.43 (d, J=2.69 hz,1H);

7.55 (dd, J=2.69, 9.04hz,1H); 7.75 (s, 1H); 8.03 (d, J=9.04 hz,1H); 8.69 (s, 1H)

Nominal Mass:

m/e = 265

Example 21

2-Hydroxy-3-methoxy-11H-indeno-[1,2-b]quinolin-8-ol (Compound 21)

(A) The same procedure as Example 5 (A) is used except that an equivalent amount of the compound of formula (IIIA), wherein Z is CH_2; R^{2a} is benzoxy; R^{3a} is methoxy; and R^{1a} and R^{4a} are hydrogen, is used in place of 4,6-dimethoxy-5-methoxymethoxyindan-1-one and an equivalent amount of the compound of formula (IIA), wherein X^1 and X^3 are hydrogen and X^{2a} is 4-methoxybenzoxy, is used in place of 6[[(4-methylphenyl)imino]methyl]-1,3-benzodioxol-5-amine to yield 2-benzoxy-3-methoxy-11H-indeno-8-(4-methoxybenzoxy)-[1,2-b]quinoline. This material was used directly in part (B).

Nominal Mass:

m/e = 443

(B) The procedure of Example 14 (B) is used to remove the hydroxy protecting groups, *i.e.*, 4-methoxybenzyl and benzyl, from the product of part (A) above and to yield 2-hydroxy-3-methoxy-11H-indeno-[1,2-b]quinolin-8-ol (46% of theory).

Nominal Mass:

m/e = 279

Example 22

2-Methoxy-3-hydroxy-11H-indeno-[1,2-b]quinolin-8-ol (Compound 22)

(A) The same procedure as Example 5 (A) is used except that an equivalent amount of the compound of formula (IIIA), wherein Z is CH_2; R^{2a} is methoxy; R^{3a} is benzoxy; and R^{1a} and R^{4a} are hydrogen, is used in place of 4,6-dimethoxy-5-methoxymethoxyindan-1-one and an equivalent amount of the compound of formula (IIA), wherein X^1 and X^3 are hydrogen and X^{2a} is 4-methoxybenzoxy, is used in place of 6[[(4-methylphenyl)imino]methyl]-1,3-benzodioxol-5-amine to yield 2-methoxy-3-benzoxy-11H-indeno-8-(4-methoxybenzoxy)-[1,2-b]quinoline. This material was used directly in part (B).

Nominal Mass:

m/e = 443

(B) The procedure of Example 14 (B) is used to remove the hydroxy protecting groups, *i.e.*, 4-methoxybenzyl and benzyl, from the product of part (A) above and to yield 2-methoxy-3-hydroxy-11H-indeno-[1,2-b]quinolin-8-ol (% of theory).

High Resolution Exact Mass: (for $C_{17}H_{13}NO_3$)

Calc.=280.0974

Found=280.0963

Example 23

2-Methoxy-11H-indeno-[1,2-b]quinolin-8-ol (Compound 23)

(A) The same procedure as Example 5 (A) is used except that an equivalent amount of the compound of formula (IIIA), wherein Z is CH_2; R^{2a} is methoxy; and R^{1a}, R^{3a}, and R^{4a} are hydrogen, is used in place of 4,6-dimethoxy-5-methoxymethoxyindan-1-one and an equivalent amount of the compound of formula (IIA), wherein X^1 and X^3 are hydrogen and X^{2a} is 4-methoxybenzoxy, is used in place of 6[[(4-methylphenyl)imino]methyl]-1,3-benzodioxol-5-amine to yield 2-methoxy-11H-indeno-8-(4-methoxybenzoxy)-[1,2-b]quinoline. This material was used directly in part (B).

Nominal Mass:

m/e = 383

B) The procedure of Example 14 (B) is used to remove the hydroxy protecting group, *i.e.*, 4-methoxybenzyl, from the product of part (A) above and to yield 2-methoxy-11H-indeno-[1,2-b]quinolin-8-ol.

High Resolution Exact Mass: (for $C_{17}H_{13}NO_2$)

Calc.=264.1025

Found=264.1036

Example 24

2-Hydroxy-11H-indeno-[1,2-b]quinolin-8-ol (Compound 24)

(A) The same procedure as Example 5 (A) is used except that an equivalent amount of the compound of formula (IIIA), wherein Z is CH_2; R^{2a} is benzoxy; and R^{1a}, R^{3a}, and R^{4a} are hydrogen, is used in place of 4,6-dimethoxy-5-methoxymethoxyindan-1-one and an equivalent amount of the compound of formula (IIA), wherein X^1 and X^3 are hydrogen and X^{2a} is 4-methoxybenzoxy, is used in place of 6[[(4-methylphenyl)imino]methyl]-1,3-benzodioxol-5-amine to yield 2-benzoxy-11H-indeno-8-(4-methoxybenzoxy)-[1,2-b]quinoline. This material was used directly in part (B).

Nominal Mass:

m/e = 459

(B) The procedure of Example 14 (B) is used to remove the hydroxy protecting groups, *i.e.*, 4-methoxybenzyl and benzyl, from the product of part (A) above and to yield 2-hydroxy-11H-indeno-[1,2-b]quinolin-8-ol.

Nominal Mass:

m/e = 249

Example 25

7,8-Dimethoxybenzofuro[3,2-b]quinolin-2-ol (Compound 25)

(A) The same procedure as Example 5 (A) is used except that an equivalent amount of the compound of formula (IIIA), wherein Z is O; R^{2a} and R^{3a} are methoxy; and R^{1a} and R^{4a} are hydrogen, is used in place of 4,6-dimethoxy-5-methoxymethoxyindan-1-one and an equivalent amount of the compound of formula (IIA), wherein X^1 and X^3 are hydrogen and X^{2a} is 4-methoxybenzoxy, is used in place of 6[[(4-methylphenyl)imino]methyl]-1,3-benzodioxol-5-amine to yield 7,8-dimethoxybenzofuro-2-(4-methoxybenzyl)-[3,2-b]quinoline. This material was used directly in part (B).

(B) The procedure of Example 14 (B) is used to remove the hydroxy protecting group, *i.e.*, 4-methoxybenzyl, from the product of part (A) above and to yield 7,8-dimethoxybenzofuro[3,2-b]quinolin-2-ol (67 % of theory).

^{1}H-300 NMR (d^6 DMSO): δ 3.65 (s, 6H); 7.06 (m, 2H); 7.17 (s, 1H); 7.4 (s, 1H); 7.73 (d, J=8.5 hz 1H); 8.01 (s, 1H); 9.74 (s, 1H)

High Resolution Exact Mass: (for $C_{17}H_{13}NO_4$)

Calc. = 296.0923

Found = 296.0926

Example 26

7,8-Dimethoxybenzofuro-1,3-dioxolo[3,2-b]quinoline (Compound 26)

This compound is prepared by the procedure of Example 1 except that an equivalent amount of the compound of formula (IIIA), wherein Z is O; R^{2a} and R^{3a} are methoxy; and R^{1a} and R^{4a} are hydrogen, is used in place of 5-methoxyindan-1-one and an equivalent amount of the compound of formula (IIA) wherein X^{2a} together with X^{3a} is methylenedioxy and X^1 is hydrogen is used in place of 6[[(4-methylphenyl)imino]methyl]-1,3-benzodioxol-5-amine to yield 7,8-dimethoxybenzofuro-1,3-dioxolo[3,2-b]quinoline (47 % of theory).

^{1}H-300 NMR ($CDCl_3$):δ 4.02 (s, 6H); 6.12 (s, 2H); 7.09 (s, 1H); 7.15 (s, 1H); 7.53 (s, 1H); 7.72 (s, 1H); 7.93 (s, 1H)

Example 27

8-Methoxybenzofuro-1,3-dioxolo[3,2-b]quinoline (Compound 27)

This compound is prepared by the procedure of Example 1 except that an equivalent amount of the compound of formula (IIIA), wherein Z is O; R^{2a} is methoxy; and R^{1a}, R^{3a} and R^{4a} are hydrogen, is used in place of 5-methoxy-indan-1-one and an equivalent amount of the compound of formula (IIA) wherein X^{2a} together with X^{3a} is methylenedioxy and X^1 is hydrogen is used in place of 6[[(4-methylphenyl)imino]methyl]-1,3-benzodioxol-5-amine to yield 7,8-dimethoxybenzofuro-1,3-dioxolo[3,2-b]quinoline (7.8 % of theory).

^{1}H-300 NMR ($CDCl_3$):δ 3.9 (s, 3H); 6.22 (s, 2H); 7.06 (dd, 1H); 7.36 (d, 1H); 7.44 (s, 1H); 7.48 (s, 1H); 8.07 (d, 1H); 8.33 (s, 1H)

Nominal Mass:

m/e = 293

Example 28

6,8-Dihydroxybenzofuro-1,3-dioxolo[3,2-b]quinoline (Compound 28)

(A) The same procedure as Example 5 (A) is used except that an equivalent amount of the compound of formula (IIIA), wherein Z is O; R^{2a} and R^{4a} are methoxymethoxy; and R^{1a} and R^{3a} are hydrogen, is used in place of 4,6-dimethoxy-5-methoxymethoxyindan-1-one and an equivalent amount of the compound of formula (IIA), wherein X^{2a} together with X^{3a} is methylenedioxy and X^1 is hydrogen, is used in place of 6[[(4-methylphenyl)imino]methyl]-1,3-benzodioxol-5-amine to yield 6,8-dimethoxymethoxybenzofuro-1,3-dioxolo[3,2-b]quinoline.

^{1}H-300 NMR ($CDCl_3$): δ 2.50 (s, 3H); 2.65 (s, 3H); 5.30 (s, 2H); 5.65 (s, 2H); 6.15 (s, 2H); 6.85 (s, 1H); 6.98 (s, 1H); 7.19 (s, 1H); 7.28 (s, 1H); 8.05 (s, 1H)

This material was used directly in part (B).

(B) The procedure of Example 14 (B) is used to remove the hydroxy protecting group, *i.e.*, 4-methoxybenzyl, from the product of part (A) above and to yield 6,8-dihydroxybenzofuro-1,3-dioxolo[3,2-b]quinoline (9.8 % of theory).

^{1}H-NMR(d_6 DMSO) δ 6.20 (s, 2H); 6.35 (s, 1H); 6.48 (s, 1H); 7.4 (s, 1H);7.42 (s, 1H); 8.15 (s, 1H); 10.15 (broad singlet, 1H, OH)

Nominal Mass:

m/e = 295

Example 29

6,8-Dihydroxybenzofuro[3,2-b]quinolin-2-ol (Compound 29)

(A) The same procedure as Example 5 (A) is used except that an equivalent amount of the compound of formula (IIIA), wherein Z is O; R^{2a} and R^{4a} are

benzoxy; and R^{1a} and R^{3a} are hydrogen, is used in place of 4,6-dimethoxy-5-methoxymethoxyindan-1-one and an equivalent amount of the compound of formula (IIA), wherein X^{2a} is 4-methoxybenzoxy X^1 and X^{3a} are hydrogen, is used in place of 6[[(4-methylphenyl)imino]methyl]-1,3-benzodioxol-5-amine to yield 6,8-dibenzoxybenzofuro-2-(4-methoxybenzoxy)-[3,2-b]quinoline. This material was used directly in part (B).

(B) The procedure of Example 14 (B) is used to remove the hydroxy protecting group, *i.e.*, 4-methoxybenzyl, from the product of part (A) above and to yield 6,8-dihydroxybenzofuro[3,2-b]quinolin-2-ol (1.4 % of theory).

^{1}H-300 NMR (d^6 DMSO): δ 5.22 (s, 2H); 5.50 (s, 2H); 6.76 (s, 1H); 7.06 (s, 1H); 7.23 -7.53 (m, 11H); 7.64 (s, 1H); 7.67 (s, 1H); 7.98 (d, 1H); 8.22 (s, 1H)

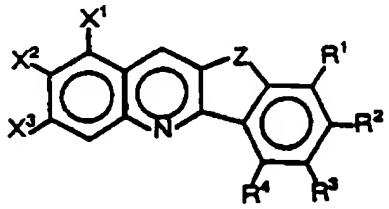
Elemental analysis: (for $C_{29}H_{21}NO_4$)

	%C	%H	%N
Found:	76.45	4.87	3.03
Calculated:	77.84	4.73	3.13

Examples 30-38

In a manner similar to the above Examples, and as described in the specification above, the following compounds of formula (I) can be prepared:

Formula (I)



(I)

Example	X^1	X^2	X^3	Z	R^1	R^2	R^3	R^4
30	H	O-Me-O		NH	OCH_3	OH	H	H
31	H	F	H	NH	H	OCH_3	NH_2	H
32	H	Cl	OH	HN	Br	OH	$OC_3H_6NH_2$	H
33	H	Br	H	O	Cl	OH	$OC_2H_4NH_2$	H
34	H	I	H	O	I	OH	OC_3H_6OH	H
35	H	OCH_3	H	O	NH_2	H	$OC_3H_6NH_2$	H
36	H	OH	H	O	F	OCH_3	OCH_3	H
37	H	O-Et-O		CH_2	H	OH	OH	H
38	H	OH	H	CH_2	H	OH	H	OH
39	H	O-Et-O		CH_2	H	O-Et-O		H

Me = CH_2 Et = C_2H_4

Example 40

Pharmaceutical formulations

(A) Transdermal System

Ingredients	Amount
Active compound	600.0 mg
Silicone fluid	450.0 mg
Colloidal silicone dioxide	25.0 mg

The silicone fluid and active compound are mixed together and the colloidal silicone dioxide is reacted with to increase viscosity. The material is then dosed into a subsequently heat sealed polymeric laminate comprised of the following: polyester release liner, skin contact adhesive composed of silicone or acrylic polymers, a control membrane which is a polyolefin (e.g. polyethylene),polyvinyl acetate or polyurethane, and an impermeable backing membrane made of a polyester multilaminate. The system described is a 10 sq. cm patch.

(B) Oral Tablet

Ingredients	Amount
Active compound	200.0 mg
Starch	20.0 mg
Magnesium Stearate	1.0 mg

The active compound and the starch are granulated with water and dried. Magnesium stearate is added to the dried granules and the mixture is thoroughly blended. The blended mixture is compressed into a tablet.

(C) Suppository

Ingredients	Amount
Active compound	150.0 mg
Theobromine sodium salicylate	250.0 mg
Witepsol S55	1725.0 mg

The inactive ingredients are mixed and melted. The active compound is then distributed in the molten mixture, poured into molds and allowed to cool.

(D) Injection

Ingredients	Amount
Active Compound	20.0 mg
Suspending Agent	q.s.
Buffering Agents	q.s.
Propylene glycol	0.4
Water for injection	0.6 mL

The active compound and buffering agents are dissolved in the propylene glycol at about 50°C. The water for injection is then added with stirring and the resulting solution is filtered, filled into an ampule, sealed and sterilized by autoclaving.

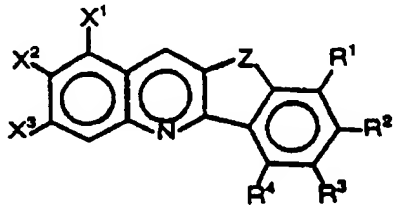
(E) Capsule

Ingredients	Amount
Active Compound	200.0 mg
Lactose	450.0 mg
Magnesium stearate	5.0 mg

The finely ground active compound is mixed with the lactose and stearate and packed into a gelatin capsule.

We claim:

1. A compound of formula (I)



(I)

wherein:

R^1 is hydrogen, hydroxy, fluoro, chloro, bromo, iodo, methoxy or amino;

R^2 is hydrogen, hydroxy, methoxy or amino;

R^3 is hydrogen, hydroxy, methoxy, methoxymethoxy, amino, $-OCONH_2$, [2(5H)-3,4-dihydro-3-oxyfuranone], 2-hydroxyethoxy, 2-aminoethoxy, 3-hydroxypropoxy or 3-aminopropoxy; or taken together with R^2 or R^4, methylenedioxy or ethylenedioxy;

R^4 is hydrogen, hydroxy or amino;

Z is $-CH_2-$, -O- or -NH-; and

a) X^1 is hydrogen;

X^2 is hydrogen, hydroxy, fluoro, chloro, bromo, iodo or methoxy; and

X^3 is hydrogen or hydroxy; or

b) X^2 taken together with X^3 is methylenedioxy or ethylenedioxy, and

X^1 is hydrogen

or a pharmaceutically acceptable salt thereof

provided that:

i) at least one of R^1 through R^4 is other than hydrogen;

ii) when R^1 is methoxy, R^2 is hydroxy or methoxy, R^3 is hydrogen or methoxy and R^4 is hydrogen;

iii) when R^2 is hydroxy, methoxy or amino, R^3 is hydrogen, hydroxy or methoxy, and R^4 is hydrogen;

iv) when R^4 is hydroxy or amino, R^1 and R^3 are hydrogen and R^2 is hydroxy or amino; and

v) when R^1 is fluoro, chloro, iodo or amino, R^2 is hydrogen, hydroxy or methoxy, R^3 is hydrogen, hydroxy or methoxy and R^4 is hydrogen.

2. A compound of Claim 1 wherein X^2 taken together with X^3 is methylenedioxy and Z is $-CH_2-$.

3. A compound of Claim 1 wherein X^2 is hydroxy, chloro or methoxy; X^3 is hydrogen or hydroxy and Z is $-CH_2-$.

4. A compound of Claim 1 wherein X^2 taken together with X^3 is methylenedioxy and Z is -O-.

5. A compound of Claim 1 wherein X^2 is hydroxy, chloro or methoxy; and X^3 is hydrogen or hydroxy and Z is -O-.

6. A compound of Claim 1 wherein X^2 taken together with X^3 is methylenedioxy and Z is -NH-.

7. A compound of Claim 1 wherein X^2 is hydroxy, chloro or methoxy; X^3 is hydrogen or hydroxy and Z is -NH-.

8. The compound of Claim 1 which is:

8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

7,8,9-trimethoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

7,8-dimethoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

7-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

7,9-dimethoxy-8-hydroxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

6,7-(1,4-dioxano)-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

7,8-(1,4-dioxano)-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

7-methoxymethoxy-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

7-hydroxy-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

7-(2-aminoethoxy)-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

7-(2-hydroxyethoxy)-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

8-methoxy-9-hydroxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

(+/-)7-[2(5H)-3,4-dihydro-3-oxyfuranone]-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

7-n-methylcarbamoyl-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline

7-methoxy-8-hydroxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline

7,8-dihydroxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline

8-hydroxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline

2,3-dimethoxy-11H-indeno-8-chloro-[1,2-b]quinoline

2,3-dimethoxy-11H-indeno-[1,2-b]quinolin-8-ol

2,3-dimethoxy-11H-indeno-8-methoxy-[1,2-b]quinolin-7-ol

7,8-dimethoxybenzofuro[3,2-b]quinolin-2-ol,

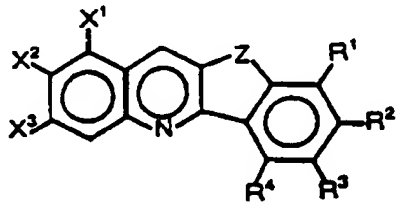
7,8-dimethoxybenzofuro-1,3-dioxolo[3,2-b]quinoline,

8-methoxybenzofuro-1,3-dioxolo[3,2-b]quinoline,

6,8-dihydroxybenzofuro-1,3-dioxolo[3,2-b]quinoline or

6,8-dihydroxybenzofuro[3,2-b]quinolin-2-ol.

9. A pharmaceutical formulation comprising a compound of formula (I),



(I)

wherein:

R^1 is hydrogen, hydroxy, fluoro, chloro, bromo, iodo, methoxy or amino;

R^2 is hydrogen, hydroxy, methoxy or amino;

R^3 is hydrogen, hydroxy, methoxy, methoxymethoxy, amino, $-OCONH_2$, [2(5H)-3,4-dihydro-3-oxyfuranone], 2-hydroxyethoxy, 2-aminoethoxy, 3-hydroxypropoxy or 3-aminopropoxy; or taken together with R^2 or R^4, methylenedioxy or ethylenedioxy;

R^4 is hydrogen, hydroxy or amino

Z is $-CH_2-$, -O- or -NH-; and

a) X^1 is hydrogen;

X^2 is hydrogen, hydroxy, fluoro, chloro, bromo, iodo or methoxy; and

X^3 is hydrogen or hydroxy; or

b) X^2 taken together with X^3 is methylenedioxy or ethylenedioxy, and

X^1 is hydrogen

or a pharmaceutically acceptable salt thereof

provided that:

i) at least one of R^1 through R^4 is other than hydrogen;

ii) when R^1 is methoxy, R^2 is hydroxy or methoxy, R^3 is hydrogen or methoxy and R^4 is hydrogen;

iii) when R^2 is hydroxy, methoxy or amino, R^3 is hydrogen, hydroxy or methoxy, and R^4 is hydrogen;

iv) when R^4 is hydroxy or amino, R^1 and R^3 are hydrogen and R^2 is hydroxy or amino; and

v) when R^1 is fluoro, chloro, iodo or amino, R^2 is hydrogen, hydroxy or methoxy, R^3 is hydrogen, hydroxy or methoxy and R^4 is hydrogen.

10. A formulation of Claim 9 wherein for the compound of forumula (I) X^2 taken together with X^3 is methylenedioxy and Z is $-CH_2-$.

11. A formulation of Claim 9 wherein for the compound of forumula (I) X^2 is chloro, hydroxy or methoxy; X^3 is hydrogen or hydroxy and Z is $-CH_2-$.

12. A formulation of Claim 9 wherein for the compound of forumula (I) X^2 taken together with X^3 is methylenedioxy and Z is -O-.

13. A formulation of Claim 9 wherein for the compound of forumula (I) X^2 is chloro, hydroxy or methoxy; X^3 is hydrogen or hydroxy and Z is -O-.

14. A formulation of Claim 9 wherein for the compound of forumula (I) X^2 taken together with X^3 is methylenedioxy and Z is -NH-.

15. A formulation of Claim 9 wherein for the compound of forumula (I) X^2 is chloro, hydroxy or methoxy; X^3 is hydrogen or hydroxy and Z is -NH-.

16. A formulation of Claim 9 wherein the compound of formula (I) is:

8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

7,8,9-trimethoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

7,8-dimethoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

7-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

7,9-dimethoxy-8-hydroxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

6,7-(1,4-dioxano)-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

6,7-(1,4-dioxano)-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

7-methoxymethoxy-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

7-hydroxy-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

7-(2-aminoethoxy)-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

7-(2-hydroxyethoxy)-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

8-methoxy-9-hydroxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

(+/-)7-[2(5H)-3,4-dihydro-3-oxyfuranone]-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

7-n-methylcarbamoyl-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline

7-methoxy-8-hydroxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline

7,8-dihydroxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline

8-hydroxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline

2,3-dimethoxy-11H-indeno-8-chloro-[1,2-b]quinoline

2,3-dimethoxy-11H-indeno-[1,2-b]quinolin-8-ol

2,3-dimethoxy-11H-indeno-8-methoxy-[1,2-b]quinolin-7-ol

7,8-dimethoxybenzofuro[3,2-b]quinolin-2-ol,

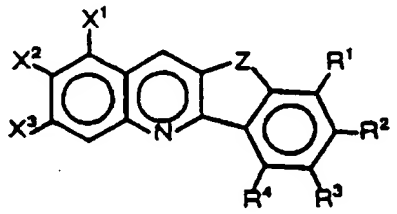
7,8-dimethoxybenzofuro-1,3-dioxolo[3,2-b]quinoline,

8-methoxybenzofuro-1,3-dioxolo[3,2-b]quinoline,

6,8-dihydroxybenzofuro-1,3-dioxolo[3,2-b]quinoline or

6,8-dihydroxybenzofuro[3,2-b]quinolin-2-ol.

17. A method of inhibiting a topoisomerase enzyme comprising contacting said enzyme with an effective inhibitory amount of a compound of formula (I)



(I)

wherein:

R^1 is hydrogen, hydroxy, fluoro, chloro, bromo, iodo, methoxy or amino;

R^2 is hydrogen, hydroxy, methoxy or amino;

R^3 is hydrogen, hydroxy, methoxy, methoxymethoxy, amino, $-OCONH_2$, [2(5H)-3,4-dihydro-3-oxyfuranone], 2-hydroxyethoxy, 2-aminoethoxy, 3-hydroxypropoxy or 3-aminopropoxy; or taken together with R^2 or R^4, methylenedioxy or ethylenedioxy;

R^4 is hydrogen, hydroxy or amino;

Z is $-CH_2-$, -O- or -NH-; and

a) X^1 is hydrogen;

X^2 is hydrogen, hydroxy, fluoro, chloro, bromo, iodo or methoxy; and

X^3 is hydrogen or hydroxy; or

b) X^2 taken together with X^3 is methylenedioxy or ethylenedioxy, and

X^1 is hydrogen

or a pharmaceutically acceptable salt thereof

provided that:

i) at least one of R^1 through R^4 is other than hydrogen;

ii) when R^1 is methoxy, R^2 is hydroxy or methoxy, R^3 is hydrogen or methoxy and R^4 is hydrogen;

iii) when R^2 is hydroxy, methoxy or amino, R^3 is hydrogen, hydroxy or methoxy, and R^4 is hydrogen;

iv) when R^4 is hydroxy or amino, R^1 and R^3 are hydrogen and R^2 is hydroxy or amino; and

v) when R^1 is fluoro, chloro, iodo or amino, R^2 is hydrogen, hydroxy or methoxy, R^3 is hydrogen, hydroxy or methoxy and R^4 is hydrogen.

18. A method of Claim 17 wherein for the compound of forumula (I), X^2 taken together with X^3 is methylenedioxy and Z is $-CH_2-$.

19. A method of Claim 17 wherein for the compound of forumula (I), X^2 is chloro, hydroxy or methoxy; X^3 is hydrogen or hydroxy and Z is $-CH_2-$.

20. A method of Claim 17 wherein for the compound of forumula (I), X^2 taken together with X^3 is methylenedioxy and Z is -O-.

21. A method of Claim 17 wherein for the compound of forumula (I), X^2 is chloro, hydroxy or methoxy; X^3 is hydrogen or hydroxy and Z is -O-.

22. A method of Claim 17 wherein for the compound of forumula (I), X^2 taken together with X^3 is methylenedioxy and Z is -NH-.

23. A method of Claim 17 wherein for the compound of forumula (I), X^2 is chloro, hydroxy or methoxy; X^3 is hydrogen or hydroxy and Z is -NH-.

24. The method of Claim 17 wherein the compound of Formula (I) is:

8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

7,8,9-trimethoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

7,8-dimethoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

7-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

7,9-dimethoxy-8-hydroxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

6,7-(1,4-dioxano)-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

6,7-(1,4-dioxano)-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

7-methoxymethoxy-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

7-hydroxy-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

7-(2-aminoethoxy)-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

7-(2-hydroxyethoxy)-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

8-methoxy-9-hydroxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

(+/-)7-[2(5H)-3,4-dihydro-3-oxyfuranone]-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

7-n-methylcarbamoyl-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline

7-methoxy-8-hydroxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline

7,8-dihydroxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline

8-hydroxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline

2,3-dimethoxy-11H-indeno-8-chloro-[1,2-b]quinoline

2,3-dimethoxy-11H-indeno-[1,2-b]quinolin-8-ol

2,3-dimethoxy-11H-indeno-8-methoxy-[1,2-b]quinolin-7-ol

7,8-dimethoxybenzofuro[3,2-b]quinolin-2-ol,

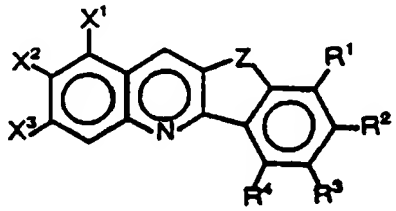
7,8-dimethoxybenzofuro-1,3-dioxolo[3,2-b]quinoline,

8-methoxybenzofuro-1,3-dioxolo[3,2-b]quinoline,

6,8-dihydroxybenzofuro-1,3-dioxolo[3,2-b]quinoline or

6,8-dihydroxybenzofuro[3,2-b]quinolin-2-ol.

25. A method of treating a tumor in a mammal comprising administering to said mammal, an effect antitumor amount of a compound of formula (I)



(I)

wherein:

R^1 is hydrogen, hydroxy, fluoro, chloro, bromo, iodo, methoxy or amino;

R^2 is hydrogen, hydroxy, methoxy or amino;

R^3 is hydrogen, hydroxy, methoxy, methoxymethoxy, amino, $-OCONH_2$, [2(5H)-3,4-dihydro-3-oxyfuranone], 2-hydroxyethoxy, 2-aminoethoxy, 3-hydroxypropoxy or 3-aminopropoxy; or taken together with R^2 or R^4, methylenedioxy or ethylenedioxy;

R^4 is hydrogen, hydroxy or amino;

Z is $-CH_2-$, -O- or -NH-; and

a) X^1 is hydrogen;
X^2 is hydrogen, hydroxy, fluoro, chloro, bromo, iodo or methoxy; and
X^3 is hydrogen or hydroxy; or

b) X^2 taken together with X^3 is methylenedioxy or ethylenedioxy, and
X^1 is hydrogen

or a pharmaceutically acceptable salt thereof

provided that:

i) at least one of R^1 through R^4 is other than hydrogen;

ii) when R^1 is methoxy, R^2 is hydroxy or methoxy, R^3 is hydrogen or methoxy and R^4 is hydrogen;

iii) when R^2 is hydroxy, methoxy or amino, R^3 is hydrogen, hydroxy or methoxy, and R^4 is hydrogen;

iv) when R^4 is hydroxy or amino, R^1 and R^3 are hydrogen and R^2 is hydroxy or amino; and

v) when R^1 is fluoro, chloro, iodo or amino, R^2 is hydrogen, hydroxy or methoxy, R^3 is hydrogen, hydroxy or methoxy and R^4 is hydrogen.

26. A method of Claim 25 wherein for the compound of forumula (I) X^2 taken together with X^3 is methylenedioxy and Z is $-CH_2-$.

27. A method of Claim 25 wherein for the compound of forumula (I) X^2 is chloro, hydroxy or methoxy; X^3 is hydrogen or hydroxy and Z is $-CH_2-$.

28. A method of Claim 25 wherein for the compound of forumula (I) X^2 taken together with X^3 is methylenedioxy and Z is -O-.

29. A method of Claim 25 wherein for the compound of forumula (I) X^2 is chloro, hydroxy or methoxy; X^3 is hydrogen or hydroxy and Z is -O-.

30. A method of Claim 25 wherein for the compound of forumula (I) X^2 taken together with X^3 is methylenedioxy and Z is -NH-.

31. A method of Claim 25 wherein for the compound of forumula (I) X^2 is chloro, hydroxy or methoxy; X^3 is hydrogen or hydroxy and Z is -NH-.

32. The method of Claim 25 wherein the compound of Formula (I) is:

8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

7,8,9-trimethoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

7,8-dimethoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

7-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

7,9-dimethoxy-8-hydroxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

6,7-(1,4-dioxano)-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

6,7-(1,4-dioxano)-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

7-methoxymethoxy-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

7-hydroxy-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

7-(2-aminoethoxy)-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

7-(2-hydroxyethoxy)-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

8-methoxy-9-hydroxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

(+/-)7-[2(5H)-3,4-dihydro-3-oxyfuranone]-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

7-n-methylcarbamoyl-8-methoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline

7-methoxy-8-hydroxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline

7,8-dihydroxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline

8-hydroxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline

2,3-dimethoxy-11H-indeno-8-chloro-[1,2-b]quinoline

2,3-dimethoxy-11H-indeno-[1,2-b]quinolin-8-ol

2,3-dimethoxy-11H-indeno-8-methoxy-[1,2-b]quinolin-7-ol

7,8-dimethoxybenzofuro[3,2-b]quinolin-2-ol,

7,8-dimethoxybenzofuro-1,3-dioxolo[3,2-b]quinoline,

8-methoxybenzofuro-1,3-dioxolo[3,2-b]quinoline,

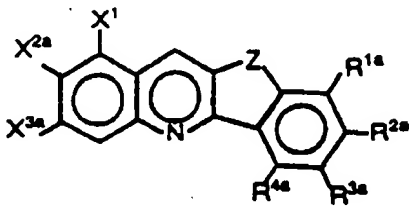
6,8-dihydroxybenzofuro-1,3-dioxolo[3,2-b]quinoline or

6,8-dihydroxybenzofuro[3,2-b]quinolin-2-ol.

33. A method of Claim 25 wherein said mammal is a human.

34. A method of Claim 25 wherein said tumor is colon or rectal tumor.

35. A compound of formula (IA)



(IA)

wherein:

R^{1a} is hydrogen, protected hydroxy, F, Cl, Br, I, methoxy or protected amino;

R^{2a} is hydrogen, protected hydroxy, methoxy;

R^{3a} is hydrogen, hydroxy, methoxy, methoxymethoxy, protected amino, $-OCONH_2$, butyrolactone-2-oxy, 2-hydroxyethoxy, 2-aminoethoxy, 3-hydroxypropoxy or 3-aminopropoxy; or taken together with R^{2a} or R^{4a}, methylenedioxy or ethylenedioxy;

R^{4a} is hydrogen or protected hydroxy;

Z is $-CH_2-$, -O- or -NH-; and

a) X^1 is hydrogen;

X^{2a} is hydrogen, protected hydroxy, F, Cl, Br, I or methoxy;

X^{3a} is hydrogen or protected hydroxy; or

b) X^{2a} taken together with X^{3a} is methylenedioxy or ethylenedioxy, and

X^1 and is hydrogen

or a pharmaceutically acceptable salt thereof

provided that:

i) at least one of R^{1a} through R^{3a} is other than hydrogen;

ii) when R^{1a} is methoxy, R^{2a} is protected hydroxy or methoxy and R^{3a} is methoxy or hydrogen;

iii) when R^{2a} is protected hydroxy or methoxy, R^{3a} is hydrogen,

hydroxy or methoxy, and R^4 is hydrogen;

iv) when R^{4a} is protected hydroxy, R^1 and R^3 are hydrogen and R^2 is protected hydroxy; and

v) when R^{1a} is fluoro, chloro, iodo or protected amino, R^2 is hydrogen, hydroxy or methoxy, R^{3a} is hydrogen, protected hydroxy or methoxy and R^4 is hydrogen.

36. A compound of Claim 35 which is:

7-methoxy-8-methoxymethoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline,

7,8-dimethoxymethoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b] quinoline,

8-methoxymethoxy-10H-1,3-dioxolo[4,5-g]indeno[1,2-b]quinoline.
2,3-dimethoxy-11H-indeno-8-(4-methoxybenzoxy)-[1,2-b]quinoline,

2,3-dimethoxy-11H-indeno-7-(4-methoxybenzoxy)-8-methoxy-[1,2-b]quinoline,

2,3-dibenzoxy-11H-indeno-8-(4-methoxybenzoxy)-[1,2-b]quinoline,

2-benzoxy-3-methoxy-11H-indeno-8-(4-methoxybenzoxy)-[1,2-b]quinoline,

2-methoxy-3-benzoxy-11H-indeno-8-(4-methoxybenzoxy)-[1,2-b]quinoline,

2-methoxy-11H-indeno-8-(4-methoxybenzoxy)-[1,2-b]quinoline,

2-benzoxy-11H-indeno-8-(4-methoxybenzoxy)-[1,2-b]quinoline,

7,8-dimethoxybenzofuro-2-(4-methoxybenzyl)-[3,2-b]quinoline,

6,8-dimethoxymethoxybenzofuro-1,3-dioxolo[3,2-b]quinoline and

6,8-dibenzoxybenzofuro-2-(4-methoxybenzoxy)-[3,2-b]quinoline.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/04611

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 D 221/18 C 07 D 471/04 C 07 D 491/048
C 07 D 491/056 C 07 D 491/147 C 07 D 491/153 A 61 K 31/47 //
(C 07 D 471/04, 221:00, 209:00), (C 07 D 491/048, 307:00, 221:00)

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 D A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	Journal of Medicinal Chemistry, vol. 14, no. 11, 1971, (Washington, DC, US), J.A. BEISLER: "Potential antitumor agents. 1. Analogs of camptothecin", pages 1116-1118, see page 1117, compounds 11,12 ---	1,9
X	Tetrahedron, vol. 46, no. 7, 1990, (Oxford, GB), R. ANTKOWIAK et al.: "Hindered N-oxides of cavity shaped molecules", pages 2445-2452, see page 2446, compound 2 ---	1
X	Tetrahedron, vol. 29, 1973, (Oxford, GB), B.A. BRADY et al.: "The configuration of aurones", pages 359-362, see page 361, compound 8 --- -/-	1

* Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
14-09-1992	21. 10. 92
International Searching Authority: EUROPEAN PATENT OFFICE	Signature of Authorized Officer

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category*	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	Journal of the Indian Chemical Society, vol. 7, 1930, (Calcutta, IN), G. SINGH et al.: "Some indenoquinoline derivatives", pages 637-645, see page 637, compound III	1
A	Journal of Medicinal Chemistry, vol. 33, no. 3, 1990, (Washington, DC, US), A.W. NICHOLAS et al.: "Plant antitumor agents. 29. Synthesis and biological activity of ring D and ring E modified analogues of camptothecin", pages 972-978, see pages 973-974, compounds 3,4,17,18; abstract	1,9
A	Journal of Heterocyclic Chemistry, vol. 10, 1973, (Provo, US), D.C. LANKIN et al.: "Synthesis of condensed heterocyclic systems V(1): 11H-indeno [1,2-b]quinolines from photochemical and acid-catalyzed rearrangements of trans-2-(2-aminobenzylidene)-1-indanones", pages 1035-1038, see page 1035, compound 7	1
A	Synthesis, no. 6, 1989, (New York, US), A. BUZAS et al.: "Synthesis and reactions of 1-acetyl-2-benzylidene-3-oxo-2,3-dihydroindoles", pages 458-461, see page 458, compound 7b	1
A	Chemical Abstracts, vol. 112, no. 7, 12 February 1990, (Columbus, Ohio, US), A. EZERSKAITE: "Synthesis of 7-bromoquindoline derivatives", see page 752, abstract no. 55658g, & IZV. KHIM. 1989, 22(1), pages 101-5, see abstract	1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/04611

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 17-34 are directed to a method of tretment of diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.